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THE INFLUENCE OF SYMPATHETIC NERVOUS CONTROL ON BLOOD FLOW THRO--ETC(U)
AUG 81 A R LIND, C A WILLIAMS AFOSR-80-0221

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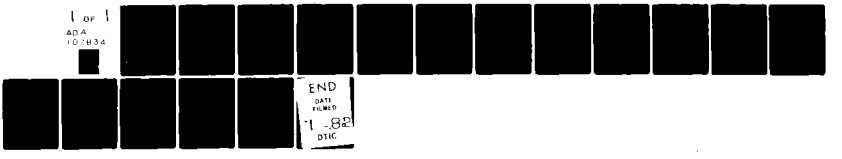

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The Influence of Sympathetic Nerves Control on Blood Flow through the Human Forearm

b. RESEARCH OBJECTIVES AND STATEMENT OF WORK

Aug. 27, 1981

The work described in this report deals with a very fundamental question in cardiovascular physiology which after some 100 years of investigation still remains open for discussion. Our project dealt with the extent of and the competition between neural (sympathetic) and metabolic control of skeletal muscle blood flow in human limbs at rest and during exercise. During fatiguing isometric exercise, changes in sympathetic tone are an integral part of the cardiovascular reflexes initiated by contracting muscle. The pressor response, one of these reflexes, is mediated by stimulation of group III and IV nerves and increased sympathetic activity. Local blood flow will be the net result of many competing factors. Metabolites released from active muscle represents the most powerful mechanism for reducing local vascular resistance and increasing blood flow. During an isometric contraction, the increase in perfusion pressure (i.e., mean blood pressure) serves as another mechanism to increase local flow. These dilating influences are counteracted by at least 3 mechanisms. First, the increase in intramuscular hydrostatic pressure due to muscular contraction diminishes the local flow by causing a physical shearing or "nipping" of local vessels. In an isometric contraction this compression of local vessels is unremitting and the compromise in the net flow becomes greater the higher the tension. Secondly, the increase in blood flow caused by the increased perfusion pressure can be opposed by a myogenic reflex. This form of autoregulation has been demonstrated in animal preparations and the human umbilical artery (which has no innervation), but as reported last year, there is no evidence to support this mechanism of control of local flow in the human forearm during isometric contractions.

Thirdly, vessels in skeletal muscle are innervated by both sympathetic cholinergic and sympathetic adrenergic fibers. The possibility of sympathetic cholinergic dilatation has been shown to play no role in the vascular responses to exercise. There still remains the possibility that cholinergic neural control causes the increased flow through a limb following instructions to or emotional preparation by the subject preceding experiments, but changes in limb blood flow are generally not seen in experienced subjects prior to experiments. It is generally accepted that an increase in sympathetic adrenergic activity causes a vasoconstriction and a decrease in adrenergic traffic diminishes the constrictor tone to vessels. In this way, there is an integrated overall control of the peripheral circulation to changing cardiovascular demands. Thus, during exercise, this mechanism accounts for vasoconstriction in the gut and skin and inactive muscles. One question that still remained unanswered was whether an adrenergic constriction occurred also to the vessels supplying the active muscles or whether there was a selective withdrawal of sympathetic tone to these muscles. The project reported here deals with an answer to this question. The blood flow responses to sustained submaximal isometric contractions has been well documented, but little was known about the changes in flow that occur in response to brief or intermittent hand-grip exercise. In order to define to what extent sympathetic control occurred in the exercising forearm, two approaches were taken. First, it was necessary to determine what sympathetic control was exerted on skeletal vessels when the forearm was at rest. Secondly, since many daily activities and certainly many of the manual activities of aircraft pilots involve brief or intermittent isometric contractions of the hand-gripping muscles, we investigated whether in fact there was any sympathetic control exerted over the exercising muscle and

if so, to what extent this was challenged by metabolic dilatation.

There are opposing views regarding what causes a change in the blood flow in "resting" limbs. Increases in blood flow have been attributed either to altered neural control or to metabolic dilatation concomitant with muscular activity. In a study by Blair, Glover and Roddie (1961), well-trained subjects showed no increase in blood flow through the forearm during rhythmic leg exercise, but untrained subjects did. The authors suggested that this increase in forearm flow might be caused by sympathetic cholinergic vasodilatation but could not exclude the possibility that it might have been of metabolic origin. In another study, the increase in flow in the "inactive" limbs of subjects exerting sustained isometric contractions was attributed to inadvertant muscular activity (Lind, Taylor, Humphreys, Kennelly and Donald, 1964). Eklund, Kaijser and Knuttsen (1974) and Eklund and Kaijser (1976, 1978) suggested that sustained isometric contractions result in an increase in blood flow to inactive limbs that is not mediated by metabolic dilatation but instead is due to β -adrenergic mechanisms. The authors reached this conclusion despite the detection of muscular activity by electromyography. The present experiments served to clarify these findings by "calibrating" one arm at low levels (1 to 10%) of the MVC using hand-grip contractions by measuring changes in e.m.g. activity and relating these to changes in forearm blood flow and oxygen uptake. This "calibrated" arm became the contralateral (or "inactive") arm and the same measurements were made on this arm during an isometric contraction (at 33% MVC) by the opposite arm. Changes in oxygen uptake or blood flow could then be related to changes in e.m.g. activity from the calibration experiments. This protocol was followed for both trained and untrained subjects and the extent of neural control was determined from experiments involving close arterial injections of both α - and β-receptor blockade and

in one case, from injection of atropine.

As stated above, in order to determine whether in fact sympathetic adrenergic constriction occurs in active muscles, we planned to measure the blood flow immediately (within 2 sec) after a brief isometric contraction. The original premise was that if the contractions were brief enough there would be little or no increase in perfusion pressure (i.e., blood pressure) and no interference on the net flow due to compression on the local vessels by the contracting muscle. If the change in forearm flow were caused solely by the release of vasoactive metabolites, then there ought to be a direct relationship between the tension exerted and the resultant dilatation. As summarized in last year's report, this proved true for tensions only up to about 60% MVC. Further increases in tension did not cause a higher blood flow. These initial findings suggested that at higher tensions a constricting influence opposed further dilatation. While the myogenic reflex might have been the mechanism eliciting this response, because at tensions of about 60% MVC the local flow is occluded by mechanical compression, there was no evidence of that to be the case from other experiments. However, the conclusion that a constricting mechanism was present was reinforced when a series of intermittent isometric contractions of 4 sec duration with intervals of 8 sec were exerted to fatigue. In this situation there was a large increase in blood pressure but with a constant forearm blood flow that reached only half-maximal levels even though there was a steadily increasing blood pressure. Again, other experiments suggested that a myogenic mechanism was not the cause of this response. Consequently, we proposed that smaller arterioles and precapillary sphincters were dilated by locally released metabolites. This dilatation was sufficient to overcome any increase in sympathetic tone at this level of the vasculature. However, as the exercise was continued and fatigue was approached, small

arteries and larger arterioles must have experienced a vasoconstriction due to an increase in sympathetic adrenergic activity and these levels of the vascular tree in the active muscle were sufficiently upstream to escape the dilating influence of released metabolites. This served as our initial explanation for the forearm flow remaining in a steady-state in the face of an ever increasing perfusion pressure. Thus we had proposed that even in active skeletal muscle there was a constant competition between metabolic dilatation and sympathetic constriction. The second part of this year's project was directed at enquiring into this possibility. Brief isometric contractions were performed in the presence of both α- and β-adrenergic antagonists. Arterial and venous plasma catecholamines and known vasodilatory metabolites were measured in order to quantify the extent of the proposed competition.

C. Status of Research

1. Neural control of circulation through resting limbs. When 17 trained subjects held sustained hand-grip contractions at tensions ranging from 1-10% MVC for 3 min, there was a direct linear relationship between tension, integrated e.m.g. and the steady-state forearm blood flow (see Fig. 1). This "calibrated" arm became the contralateral or "resting" arm when the other arm held an isometric hand-grip at 33% MVC for 2 min. Again forearm blood flow and e.m.g. were measured on the contralateral arm, and on separate occasions, the blood pressure was recorded. In 11 of the subjects, there was no evidence of muscular activity in the resting arm, as judged by the e.m.g., during the 2 min contraction with the opposite arm. In these subjects there was no increase in blood flow during the contraction. At the onset of the contraction, there was a tendency for the blood flow to decrease in the contralateral arm. There was a quick increase in the mean blood pressure at the onset of exercise and then a steady increase in pressure as the exercise continued. Resistance was almost doubled in the contralateral arm in these subjects. The other 6 trained subjects showed some e.m.g. activity and an increase in forearm blood flow. There was a direct linear relationship between the forearm blood flow and e.m.g. activity. There was a good correspondence between the flow seen in response to this inadvertant muscle activity and e.m.g. to the flows and e.m.g. activity measured during the calibration experiment. The oxygen uptake by the forearm was measured in 3 of these subjects. It increased from a resting value of 0.22 ml . 100 gm . min^{-1} at rest to 0.63 ml . 100 gm . min^{-1}. The average blood flow changed from 2.5 to 5.9 ml . 100 ml . min^{-1}. The e.m.g. activity corresponded to a tension of about 4% MVC. We also performed similar experiments with 6 naive subjects. Four of these subjects showed an initial (i.e. the first 30 sec of the opposite arm contraction) increase in forearm flow with a slightly

decreased forearm vascular resistance. No e.m.g. activity was detected from the forearms of these subjects except during the initial part of the contraction. As the contraction proceeded, blood flow fell steadily and was lower during the last 30 sec of exercise than at rest. The other 2 subjects showed variable responses to exercise but e.m.g. activity and blood flow always changed similarly. These subjects were able voluntarily to relax their contralateral arms, when so instructed, during the exercise.

The blood flow in the contralateral (resting) arm either decreased or stayed constant during isometric contractions with the opposite arm. When an increase in the "resting" forearm flow was seen, it was always accompanied by inadvertant muscular activity, measured by changes in the e.m.g. signal, and by an increase in the oxygen usage by the forearm. These results are similar to those from other experiments where the forearm blood flow was found to decrease in response to rhythmic leg exercise (provided the severity of the exercise did not encroach on thermoregulatory needs). The conclusions from both types of studies indicate that the decrease in flow was controlled by sympathetic constriction. When forearm flow did increase, it was mediated by the release of metabolic dilators. As mentioned in the previous section, some investigators believe there is an inevitable increase in blood flow in the contralateral arm during isometric contractions. This increase in flow is supposed to be mediated by β-adrenergic receptors. We looked into this possibility. Four of our subjects performed the contralateral arm contractions before and after close arterial infusion of Inderal (propranolol). During the control contraction, forearm blood flow remained constant for the 2 min period at the same level as the pre-contraction flow. Forearm vascular resistance increased 1.5 fold during the 2 min contraction. The same pattern in forearm blood flow and resistance was seen after infusion of Inderal. The

average blood flow tended to be higher than in the control experiment and remained so, in parallel, during the contraction. Accordingly, the peripheral resistance tended to be lower than and in parallel to that found in the control experiment. In order to pursue the role of the sympathetic system further, the same experiments were performed in the presence of close arterial infusions of Regitine (phentolamine). Five subjects participated in this series of experiments. Forearm flow immediately tripled upon infusion of the α-blocker. The blood flow in the contralateral arm increased linearly throughout the contraction to almost double its resting value. Mean blood pressure increased similarly following α-blockade in the forearm as it did in the control experiments. The peripheral resistance did not change from its resting level during the first 1.5 min of contralateral arm grip, and then decreased slightly for the remainder of exercise. Three of the subjects performed the contralateral grip after infusion of both Inderal and Regitine to block both β- and α-receptors. The results were similar to those when only Regitine had been infused. The important finding from these experiments was the consistent increase in vascular resistance during the contraction in the presence of β-blockade indicating β-adrenergic receptors were not responsible for the contralateral arm blood flow during isometric exercise. This is not to say that the sympathetic adrenergic system plays no role in the forearm blood flow response in the resting arm. Indeed, because the vascular resistance was unchanged from resting values following α-adrenergic receptor blockade during contralateral hand-grip, it is obvious that the vasoconstriction which occurs in the resting arm is mediated through sympathetic α-adrenergic fibers. The conclusions put forth by Eklund and her colleagues seem untenable since it is known that β-receptors are stimulated by epinephrine and could only be activated when the circulating levels of epinephrine become sufficient. There is no known nerve ending source for epinephrine. The changes in circulating epinephrine

during isometric exercise is small and because of the lag time in its release from the adrenal medulla and its circulation it cannot explain the possible activation of β-receptors to induce the prompt dilatation that occurs in some subjects during contralateral hand-grip.

2. The Competition Between Neural and Metabolic Control of Blood Flow in the Active Forearm

While the above series of experiments described the neural control of blood flow in the resting forearm, there still remained the question of whether sympathetic vasoconstriction occurred in the exercising forearm. Two types of experiments were performed in order to answer this question. Both involved brief hand-grip contractions. In the first series, a single contraction was exerted for only 2 sec at tensions ranging from 10-80% MVC. Five subjects participated in this series and each performed this type of exercise under control conditions and in the presence of either α- or β-blocking agents. In the control condition, there was a direct relationship between the first post-contraction blood flow (measured 2 sec after the release of tension and taken to be a reflection of exercise induced vasodilatation) and the tension up to 60% of the subjects' MVC. Thereafter, even though the tension of the next contraction exceeded 60% MVC, there was no further increase in this first post-contraction flow. The flow increased to about 15 ml. min^{-1} . 100 ml^{-1} at its highest level (following a 2 sec contraction at either 60 or 80% MVC). This result is identical to those reported by our laboratory in last year's annual report. The same hyperbolic relationship with almost the same absolute blood flows resulted when subjects repeated the exercise following close arterial injection of 1.0 mg. propranolol. However, when the α-blocking agent, phentolamine, was administered (0.5 mg), resting flow immediately increased by 2.5 fold and there was then a direct, linear relationship between flow and tension, reaching a level of about 26 ml . min^{-1} . 100 ml^{-1} after a 2 sec contraction at 80% MVC. These results suggest that α-adrenergic mediated sympathetic vasoconstriction occurs in response to contractions as short as 2 sec. These results were somewhat surprising because

there were no systemic indications (i.e. increases in blood pressure or heart rate) that a change in sympathetic activity had occurred during these very brief contractions which were not fatiguing. These results also support the conclusion from the contralateral arm experiments that there is no neural vasodilatation of human forearm vessels controlled by β-adrenergic mechanisms.

In the second type of experiment, the same subjects exerted hand-grip contractions at 60% MVC in a repetitive manner until fatigue was reached. Each contraction was held for 4 sec and there were 8 sec of relaxation permitted between each contraction. This exercise was also performed following close arterial injection of either propranolol or phentolamine. As we reported last year, when this type of exercise was continued to fatigue, blood pressure increased as it did in response to sustained isometric contractions held to fatigue, but forearm blood flow remained constant for the duration of the exercise at a level of 20-24 ml . min^{-1} . 100 ml^{-1}, only half the maximal flow possible through the forearm. The same results were seen after infusion of propranolol. But following infusion of phentolamine, forearm blood flow increased progressively as fatigue was approached, and reached its highest level, about 39 ml . min^{-1} . 100 ml^{-1}, at fatigue. This flow is approximately the maximal flow possible through the human forearm. This blockade of α-receptors by phentolamine was successfully blocked with phenylephrine, an α-agonist. These results are supportive of the concept that sympathetic vasoconstriction occurred in active skeletal muscle. We also measured changes in arterial and venous plasma catecholamines. If there were an increased sympathetic activity in the active forearm, then the venous plasma concentrations of norepinephrine would be expected to rise during exercise, while arterial levels of catecholamines would not be expected to change very much. This was the case. Total (epinephrine and norepinephrine) catecholamine

concentration in the arterial plasma from 3 subjects changed from a resting level of 25.5 pg . ml^{-1} to 159 pg . ml^{-1} at fatigue. In contrast, the total catecholamine concentration in the venous plasma increased from a resting level of 45 pg . ml^{-1} to one of 983 pg . ml^{-1} at fatigue. Almost all of the catecholamine found in the venous plasma was in the form of norepinephrine. Most of the change in the catecholamines in arterial plasmas was in the form of epinephrine. These data are important for two reasons. First, the changes in arterial catecholamines found as epinephrine represent the alterations in adrenal medulla activity during fatiguing intermittent contractions. Secondly, because practically all the venous catecholamines were found as norepinephrine, this signifies an increase in α-adrenergic activity serving the vessels in the active muscle, and the levels of norepinephrine represent a direct measurement of this increased activity. These results support the proposal put forward previously by our laboratory that the steady-state forearm blood flow seen in response to fatiguing intermittent contractions is due to the escape of pre-capillary sphincters and smaller arterioles from vasoconstrictor control by metabolic dilators and the increased constrictor tone on larger arterioles and small arteries. If this competition between metabolic and neural mechanisms is operating to control the local flow in active muscles, then supporting evidence should be found in the pattern of change in venous concentrations of known vasodilators. Only small changes occurred in the osmolarity of venous plasma during fatiguing exercise, thus it is unlikely that osmotically active substances were involved with the dilatation induced by this type of isometric contraction. In contrast, venous plasma K^+ increased in response to the first few contractions from resting levels of 3.6 mEq . L^{-1} to 4.4 to 4.9 mEq . L^{-1} and then remained at a constant level throughout the remainder of the fatiguing exercise, much like the pattern of the forearm blood flow. Arterial concentrations of K^+ did not change. A very different pattern was

seen in the changes of venous plasma ATP. As the intermittent contractions continued and fatigue was approached, the levels of ATP continuously increased and reached the highest concentration at fatigue. Clearly both K^+ and ATP increased in sufficient quantities to account for the dilatation of forearm flow to levels of 20-24 ml . min^{-1} . 100 ml^{-1}. Both substances have been well documented as vasodilators. Because K^+ increased initially during the first few contractions and then remained in a steady-state, it can be assumed that a constant amount of K^+ was released by each 4 sec contraction and an equally constant amount was washed out of the interstitial space during the 8-sec relaxation period. It was unexpected that the change in the concentration of ATP correlated with not only the change in arterial blood pressure but also the change in total venous catecholamines and venous norepinephrine. The appearance of ATP in increased amounts during the early part of intermittent exercise supports its role as a vasodilator substance during isometrics. The fact that ATP was released in increasing concentrations as successive contractions continued and reached its peak concentration at fatigue suggests quite strongly that it may well be the vasodilator substance competing with the increased release of norepinephrine for the control of pre-capillary sphincters and small arterioles. Larger arterioles and small arteries, removed by distance from the influences of at least K^+ and ATP (and probably other substances not identified in these experiments), would remain under increased vasoconstrictor tone and give rise to the steady-state blood flow seen during the fatiguing exercise. These results support our proposal that sympathetic mediated neural control is exerted on the vessels in the active muscle. It appears from these results that metabolic mechanisms account for a dilatation that approximates about half the maximal flow possible and that α-adrenergic mechanisms induce a constriction that prevents the flow from increasing a further 20 ml . min^{-1} . 100 ml^{-1}.

d. LIST OF PUBLICATIONS

1. The blood flow through the "resting" arm during hand-grip contractions. A. R. Lind, T. E. Dahsm, C. A. Williams, and J. S. Petrofsky. Circ. Res. 48 (Suppl. 1): 104-109, 1981.

2. The forearm blood flow during intermittent hand-grip isometric exercise. C. A. Williams, J. G. Mudd, and A. R. Lind. Circ. Res. 48 (Suppl. 1): 110-117, 1981.

3. Neural and metabolic control of forearm blood flow during brief isometric contractions. A. R. Lind, J. G. Mudd, and C. A. Williams. In preparation.

4. The control of blood flow through the contralateral arm during sustained hand grip contractions. T. E. Dahms, A. R. Lind, J. S. Petrofsky, and C. A. Williams. In preparation.

ABSTRACTS

1. α-Adrenergic and metabolic control of forearm blood flow during intermittent hand-grip contractions. C. A. Williams and A. R. Lind. Physiologist 23: 157, 1980.

2. The relationship between forearm blood flow and the release of ATP and adenosine during isometric exercise. A. R. Lind and C. A. Williams. Fed. Proc. 40: 598, 1981.

e. PROFESSIONAL PERSONNEL

A. R. Lind (*Principal Investigator*)

J. S. Petrofsky

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T. E. Dahms

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The role of neurally mediated (sympathetic) vasoconstriction and metabolic dilatation has been examined in both exercising and resting forearms of human volunteers. To examine this competition in the resting forearm, the arms were "calibrated" for changes in blood flow, integrated e.m.g. and oxygen uptake at low sustained isometric tensions (1-10% MVC). The "calibrated" arm became the contralateral ("resting") arm during a sustained isometric hand-grip contraction at 33

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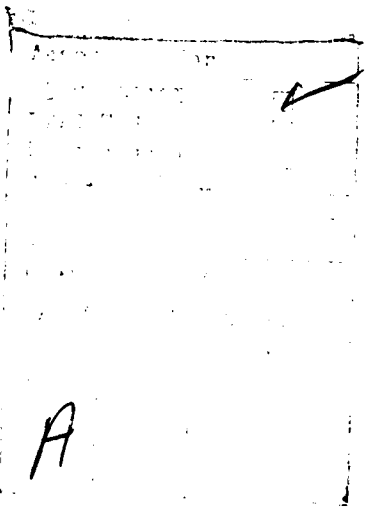
MVC for 2 min with the opposite arm. There was no significant increase in forearm blood flow in the contralateral arm in two-thirds of both trained and naive subjects. Small increases in flow were matched by increases in e.m.g. activity. The remainder of subjects demonstrated almost a doubling of blood flow in the contralateral arm during the second min of the contraction but this change was also accompanied by appropriate increases in e.m.g. activity. Use of either α-adrenergic or β-adrenergic blocking agents indicated that increased α-adrenergic activity mediated changes in vascular resistance during isometric exercise. There was no detectable control of forearm flow exerted by β-adrenergic receptors.

In order to determine the competition between neural and metabolic control of forearm flow, subjects performed brief, intermittent hand-grip contractions. The extent of sympathetic neural activity was determined by measurement of arterial and venous plasma epinephrine and norepinephrine from the exercising forearm. Metabolic influence over local flow was determined from measurements of venous plasma K^+, osmolarity and ATP. When intermittent contractions at 60% MVC were exerted in a repetitive fashion, mean arterial pressure rose to 155-160 mm Hg, but forearm flow remained at a steady level averaging 20-24 ml . min^{-1}, only about half the maximal possible flow through the forearm. There was no difference in the blood flow from control levels in response to β-adrenergic blockade, but when the exercise was repeated after α-adrenergic receptor blockade, forearm flow steadily increased to near maximal levels at fatigue. Venous plasma K^+ increased initially from resting levels and then remained in a steady-state for the duration of the exercise. Venous osmolarity changed little, while venous ATP increased steadily throughout the exercise, reaching peak levels at fatigue. Venous norepinephrine increased steadily throughout the exercise, reaching peak levels at fatigue. Little change was seen in arterial levels of norepinephrine.



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